#30
Dra
1/31/02

JC813 U.S. PTO
11/21/01

PATENT
Attorney's Docket Number: 07681.0017-01
CUSTOMER NUMBER: 22,852

jc971 U.S. PTO
09/989125
11/21/01

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

ASSISTANT COMMISSIONER FOR PATENTS
Washington, D.C. 20231

Prior Application: Art Unit: 1632 Examiner: D. Crouch

SIR: This is a request for filing a

■ Continuation □ Continuation-in-Part □ Divisional Application under 37 C.F.R. § 1.53(b) of pending prior application Serial No. 09/650,285 filed August 29, 2000 of Keith Campbell et al. for UNACTIVATED OOCYTES AS CYTOPLAST RECIPIENTS FOR NUCLEAR TRANSFER.

1. ■ Enclosed is a complete copy of the prior application including the oath or Declaration and drawings, if any, as originally filed. I hereby verify that the attached papers are a true copy of prior application Serial No. 08/803,165 as originally filed on February 19, 1997.

2. □ Enclosed is a substitute specification under 37 C.F.R. § 1.125.

3. □ Cancel Claims ____.

4. ■ A Preliminary Amendment is enclosed.

5. ■ The filing fee is calculated on the basis of the claims existing in the prior application as amended at 3 and 4 above.

Basic Application Filing Fee					$740	$ 740
	Number of Claims		Basic	Extra Claims		
Total Claims	1	-	20		x $18	
Independent Claims	1	-	3		x $84	
□ Presentation of Multiple Dep. Claim(s)					+$280	
Subtotal						$ 740
Reduction by 1/2 if small entity						-
TOTAL APPLICATION FILING FEE						$ 740

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

6. ■ A check in the amount of $740.00 to cover the filing fee is enclosed.

7. ■ The Commissioner is hereby authorized to charge any fees which may be required including fees due under 37 C.F.R. § 1.16 and any other fees due under 37 C.F.R. § 1.17, or credit any overpayment during the pendency of this application to Deposit Account No. 06-0916.

8. ■ Amend the specification by inserting before the first line, the sentence:

--This is a ■ continuation of application Serial No. 09/650,285 filed August 29, 2000, which is a continuation of application Serial No. 08/803,165, filed February 19, 1997, which claims the benefit of PCT/GB96/02098 , filed on August 30, 1996, and British application GB 9517779.6, filed on August 31, 1995, all of which are incorporated herein by reference.--

9. ■ New formal drawings are enclosed.

10. ■ The prior application is assigned of record to: Roslin Institute (Edinburgh) ; The Minister of Agriculture, Fisheries and Food; and Biotechnology & Biological Sciences Research Council.

11. ■ Priority of application Serial Nos. PCT/GB96/02098 , filed on August 30, 1996, and GB 9517779.6, filed on August 31, 1995 in Great Britain, is claimed under 35 U.S.C. § 119 or § 365. A certified copy

□ is enclosed or ■ is on file in the prior application.

12. □ A verified statement claiming small entity status

□ is enclosed or □ is on file in the prior application.

13. ■ An associate power of attorney in the prior application is to at least one of the following: FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P., Douglas B. Henderson, Reg. No. 20,291; Ford F. Farabow, Jr., Reg. No. 20,630; Arthur S. Garrett, Reg. No. 20,338; Donald R. Dunner, Reg. No. 19,073; Brian G. Brunsvold, Reg. No. 22,593; Tipton D. Jennings, IV, Reg. No. 20,645; Jerry D. Voight, Reg. No. 23,020; Laurence R. Hefter, Reg. No. 20,827; Kenneth E. Payne, Reg. No. 23,098; Herbert H. Mintz, Reg. No. 26,691; C. Larry O'Rourke, Reg. No. 26,014; Albert J. Santorelli, Reg. No. 22,610; Michael C. Elmer, Reg. No. 25,857; Richard H. Smith, Reg. No. 20,609; Stephen L. Peterson, Reg. No. 26,325; John M. Romary, Reg. No. 26,331; Bruce C. Zotter, Reg. No. 27,680; Dennis P. O'Reilley, Reg. No. 27,932; Allen M. Sokal, Reg. No. 26,695; Robert D. Bajefsky, Reg.

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

No. 25,387; Richard L. Stroup, Reg. No. 28,478; David W. Hill, Reg. No. 28,220; Thomas L. Irving, Reg. No. 28,619; Charles E. Lipsey, Reg. No. 28,165; Thomas W. Winland, Reg. No. 27,605; Basil J. Lewris, Reg. No. 28,818; Martin I. Fuchs, Reg. No. 28,508; E. Robert Yoches, Reg. No. 30,120; Barry W. Graham, Reg. No. 29,924; Susan Haberman Griffen, Reg. No. 30,907; Richard B. Racine, Reg. No. 30,415; Thomas H. Jenkins, Reg. No. 30,857; Robert E. Converse, Jr., Reg. No. 27,432; Clair X. Mullen, Jr., Reg. No. 20,348; Christopher P. Foley, Reg. No. 31,354; John C. Paul, Reg. No. 30,413; David M. Kelly, Reg. No. 30,953; Kenneth J. Meyers, Reg. No. 25,146; Carol P. Einaudi, Reg. No. 32,220; Walter Y. Boyd, Jr., Reg. No. 31,738; Steven M. Anzalone, Reg. No. 32,095; Jean B. Fordis, Reg. No. 32,984; Roger D. Taylor, Reg. 28,992; Barbara C. McCurdy, Reg. No. 32,120; James K. Hammond, Reg. No. 31,964; Richard V. Burgujian, Reg. No. 31,744; J. Michael Jakes, Reg. No. 32,824; Thomas W. Banks, Reg. No. 32,719; Christopher P. Isaac, Reg. No. 32,616; Bryan C. Diner, Reg. No. 32,409; M. Paul Barker, Reg. No. 32,013; Andrew Chanho Sonu, Reg. No. 33,457; David S. Forman, Reg. No. 33,694; Vincent P. Kovalick, Reg. No. 32,867; James W. Edmondson, Reg. No. 33,871; Michael R. McGurk, Reg. No. 32,045; Joann M. Neth, Reg. No. 36,363; Gerson S. Panitch, Reg. No. 33,751; Cheri M. Taylor, Reg. No. 33,216; Charles E. Van Horn, Reg. No. 40,266; Linda A. Wadler, Reg. No. 33,218; Jeffrey A. Berkowitz, Reg. No. 36,743; Michael R. Kelly, Reg. No. 33, 921; James B. Monroe, Reg. No. 33,971; Doris Johnson Hines, Reg. No. 34,629; Allen R. Jensen, Reg. No. 28,224; Lori Ann Johnson, Reg. No. 34,498; and David A. Manspeizer, Reg. No. 37,540.

14. ☐ The power appears in the original declaration of the prior application.

15. ■ Since the power does not appear in the original declaration, a copy of the power in the prior application is enclosed.

16. ■ Please address all correspondence to FINNEGAN, HENDERSON, FARABOW, GARRETT and DUNNER, L.L.P., 1300 I Street, N.W., Washington, D.C. 20005-3315. **Customer Number 22,852**.

17. ☐ Recognize as associate attorney _____

18. ■ Also enclosed is a Request Under 37 C.F.R. §1.607 for Interference with U.S. Patent 6,215,041 to Stice et al. with Exhibits A-E.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

PETITION FOR EXTENSION. If any extension of time is necessary for the filing of this application, including any extension in the parent application, Serial No. 09/650,285, filed August 29, 2000, for the purpose of maintaining copendency between the parent application and this application, and such extension has not otherwise been requested, such an extension is hereby requested, and the Commissioner is authorized to charge necessary fees for such an extension to our Deposit Account No. 06-0916. A duplicate copy of this paper is enclosed for use in charging the deposit account.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Date: November 21, 2001

By: [signature]

Kenneth J. Meyers
Reg. No. 25,146
Tel: (202) 408-4033
Fax: (202) 408-4400
Email: meyersk@finnegan.com

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

PATENT
Attorney Docket No.07681.0017-01
(710/205C)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
CAMPBELL et al.	)	Group Art Unit: 1632
	)	
Serial No.: TO BE ASSIGNED	)	Examiner: D. Crouch
	)	
Filed: November 21, 2001	)	
	)	
For: UNACTIVATED OOCYTES AS CYTOPLAST RECIPIENTS FOR NUCLEAR TRANSFER	)	

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

SUPPORT FOR APPLICANTS' CLAIM 19

Limitations in Applicants' claim 19	Support in Application
19. A method of cloning	This invention relates to the generation of animals including but not being limited to genetically selected and/or modified animals, and to cells useful in their generation. (Pg. 1, lines 4-7). . . . all animals produced from embryos prepared by the invention should transmit the relevant genetic modification through the germ line as each animal is derived from a single nucleus; (Pg. 6, lines 9-12). 13. A method of preparing an animal, the method comprising: (a) reconstituting an animal embryo as claimed in any preceding claim; (b) causing an animal to develop to term from the embryo; and (c) optionally, breeding from the animal so formed. (Page 30, lines 17-25).

Limitations in Applicants' claim 19	Support in Application
	Since the demonstration of embryo cloning in amphibians, similar techniques have been applied to mammalian species. These techniques fall into two categories: 1) transfer of a donor nucleus to a matured metaphase II oocyte which has had its chromosomal DNA removed and 2) transfer of a donor nucleus to a fertilised one cell zygote which has had both pronuclei removed. In ungulates the former procedure has become the method of choice as no development has been reported using the latter other than when pronuclei are exchanged. . . . equivalent totipotent nuclei from a single individual could, when transferred to an enucleated egg, give rise to "genetically identical" individuals. (Page 1, line 32 - page 2, line 1).
a non-human mammal	In principle, the invention is applicable to all animals, including birds such as domestic fowl, amphibian species and fish species. In practice, however, it will be to non-human animals, especially non-human mammals, particularly placental mammals, that the greatest commercially useful applicability is presently envisaged. It is with ungulates, particularly economically important ungulates such as cattle, sheep, goats, water buffalo, camels, and pigs that the invention is likely to be most useful, both as a means for cloning animals and as a means for generating transgenic animals. It should also be noted that the invention is also likely to be applicable to other economically important animal species such as, for example, horses, llamas or rodents, e.g. rats or mice, or rabbits. (Page 5, lines 14-28).
by nuclear transfer comprising:	In the method of the invention described above, a diploid nucleus is transferred from a donor into the enucleated recipient oocyte. (Page 7, lines 16-18).

Limitations in Applicants' claim 19	Support in Application
	Most conveniently, nuclear transfer is effected by fusion. (Page 10, lines 28-29).
(i) inserting a nucleus	Once suitable donor and recipient cells have been prepared, it is necessary for the nucleus of the former to be transferred to the latter. (Page 10, lines 26-28).
of a non-human mammalian differentiated somatic cell,	Subject to the above, it is believed that there is no significant limitation on the cells that can be used in nuclear donors: fully or partially differentiated cells or undifferentiated cells can be used as can cells which are cultured *in vitro* or abstracted *ex vivo*. The only limitation is that the donor cells have normal DNA content and be karyotypically normal. (Page 8, lines 13-19). Exposure of cells to fusion-promoting chemical such as polyethylene glycol or other glycols is a routine procedure for the fusion of somatic cells, but it has not been widely used with embryos. (Page 11, lines 6-10).
which has passed start in the mitotic cell cycle and is in the G1 phase of the cell cycle,	In order to maintain the correct ploidy of the reconstructed embryo the donor nucleus must be diploid (i.e., in the G0 or G1 phase of the cell cycle) at the time of fusion. (Page 10, lines 21-24). The mitotic cell cycle has four distinct phases, G, S, G2 and M. The beginning event in the cell cycle, called start, takes place in the G1 phase and has a unique function. The decision or commitment to undergo another cell cycle is made at start. Once a cell has passed through start, it passes through the remainder of the G1 phase, which is the pre-DNA synthesis phase. (Page 7, lines 26-32). . . . therefore donors may be either in the G1 phase or preferably, as is the subject of our co-pending PCT patent application No. PCT/GB96/02099 filed today (claiming

Limitations in Applicants' claim 19	Support in Application
	priority from GB 9517780.4), in the G0 phase of the cell cycle. (Page 7, line 21-24).
into an unactivated,	After enucleation, the donor nucleus is introduced either by fusion to donor cells under conditions which do not induce oocyte activation or by injection under non-activating conditions. (Page 10, lines 18-21). In a preferred embodiment of the invention, fusion of the oocyte karyoplast couplet is accomplished in the absence of activation by electropulsing in 0.3M mannitol solution or 0.27M sucrose solution; alternatively the nucleus may be introduced by injection in a calcium free medium. The age of the oocytes at the time of fusion/injection and the absence of calcium ions from the fusion/injection medium prevent activation of the recipient oocyte. (Page 12, lines 1-8).
metaphase II-arrested,	Recipient cells useful in the invention are enucleated oocytes which are arrested in the metaphase of the second meiotic division. (Page 8, lines 29-31).
non-human mammalian enucleated oocyte	In principle, the invention is applicable to all animals, including birds such as domestic fowl, amphibian species and fish species. In practice, however, it will be to non-human animals, especially non-human mammals, particularly placental mammals, that the greatest commercially useful applicability is presently envisaged. It is with ungulates, particularly economically important ungulates such as cattle, sheep, goats, water buffalo, camels, and pigs that the invention is likely to be most useful, both as a means for cloning animals and as a means for generating transgenic animals. It should also be

Limitations in Applicants' claim 19	Support in Application
	noted that the invention is also likely to be applicable to other economically important animal species such as, for example, horses, llamas or rodents, e.g. rats or mice, or rabbits. (Page 5, lines 14-28). According to a first aspect of the present invention there is provided a method of reconstituting an animal embryo, the method comprising transferring a diploid nucleus into an oocyte which is arrested in the metaphase of the second meiotic division without concomitantly activating the oocyte, keeping the nucleus exposed to the cytoplasm of the recipient for a period of time sufficient for the reconstituted embryo to become capable of giving rise to a live birth and subsequently activating the reconstituted embryo while maintaining correct ploidy. At this stage, the reconstituted embryo is a single cell. (Page 5, lines 1-12). It is preferred that the recipient be enucleated (Page 9, line 6).
of the same species	The invention is equally applicable in the production of transgenic, as well as non-transgenic animals. (Page 5, lines 30-31).
to reconstruct an embryo;	According to a first aspect of the present invention there is provided a method of reconstituting an animal embryo . . . . (Page 5, lines 1-3). Table 5 shows induction of pregnancy following transfer of all morula/blastocyst stage reconstructed embryos to the uterine horn of synchronised final recipient blackface ewes. (Page 28, lines 1-4).

Limitations in Applicants' claim 19	Support in Application
(ii) maintaining the reconstructed embryo without activation	After enucleation, the donor nucleus is introduced either by fusion to donor cells under conditions which do not induce oocyte activation or by injection under non-activating conditions. (Page 10, lines 18-21). It has now been found that nuclear transfer into an oocyte arrested in metaphase II can give rise to a viable embryo if normal ploidy (i.e., diploidy) is maintained and if the embryo is not activated at the time of nuclear transfer. The delay in activation allows the nucleus to remain exposed to the recipient cytoplasm.
for a sufficient time to allow the reconstructed embryo to become capable of developing to term;	Subsequently, the fused reconstructed embryo, which is generally returned to the maturation medium, is maintained without being activated so that the donor nucleus is exposed to the recipient cytoplasm for a period of time sufficient to allow the reconstructed embryo to become capable, eventually, of giving rise to a live birth (preferably of a fertile offspring). (Page 12, lines 21-28).
(iii) activating the resultant reconstructed embryo;	When it is time for activation, any conventional or other suitable activation protocol can be used. (Page 13, lines 5-6). The optimum period of time before activation varies from species to species and can readily be determined by experimentation. (Page 12, lines 30-32).
(iv) culturing said activated, reconstructed embryo to blastocyst; and	Aside from the issue of yield-improving expediencies, the reconstituted embryo may be cultured, *in vivo* and *in vitro* to blastocyst. (Page 17, line 1-3).

Limitations in Applicants' claim 19	Support in Application
	The process can be regarded as involving five steps: * * * (4) culture, *in vivo* or *in vitro*, to blastocyst; (Page 19, lines 14-24).
(v) transferring	After screening, if screening, has taken place, the blastocyst embryo is allowed to develop to term. This will generally be *in vivo*. If development up to blastocyst has taken place *in vitro*, then transfer into the final recipient animal takes place at this stage. (Page 18, lines 5-9). The process can be regarded as involving five steps: * * * (5) transfer if necessary to final recipient. (Page 19, lines 14-28).
said cultured, reconstructed embryo	These results show that: * * * iii) reconstructed embryos or enucleated pulsed oocytes can be cultured in maturation medium and do not undergo spontaneous activation; (Page 24, line 32-page 25, line 12).
to a host non-human mammal	In principle, the invention is applicable to all animals, including birds such as domestic fowl, amphibian species and fish species. In practice, however, it will be to non-human animals, especially non-human mammals, particularly placental mammals, that the greatest commercially useful applicability is presently envisaged. It is with ungulates, particularly economically important ungulates such as cattle, sheep, goats, water buffalo, camels,

Limitations in Applicants' claim 19	Support in Application
	and pigs that the invention is likely to be most useful, both as a means for cloning animals and as a means for generating transgenic animals. It should also be noted that the invention is also likely to be applicable to other economically important animal species such as, for example, horses, llamas or rodents, e.g. rats or mice, or rabbits. (Page 5, lines 14-28).
of the same species	The invention is equally applicable in the production of transgenic, as well as non-transgenic animals. (Page 5, lines 30-31).
such that the reconstructed embryo develops to term.	According to a third aspect of the invention, there is provided a method of preparing an animal, the method comprising: (a) reconstituting an animal embryo as described above; and (b) causing an animal to develop to term from the embryo; and (c) optionally, breeding from the animal so formed. (Page 15, lines 19-27). The second step (b) in the method of this aspect of the invention is to cause an animal to develop to term from the embryo. (Page 15, lines 31-33). According to a fourth aspect of the invention, there is provided an animal prepared as described above. (Page 20, lines 22-23).

PATENT
Attorney Docket No.07681.0017-01
(710/205C)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
CAMPBELL et al.	)	Group Art Unit: 1632
	)	
Serial No.: TO BE ASSIGNED	)	Examiner: D. Crouch
	)	
Filed: November 21, 2001	)	
	)	
For: UNACTIVATED OOCYTES AS CYTOPLAST RECIPIENTS FOR NUCLEAR TRANSFER	)	

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

REQUEST UNDER 37 C.F.R. § 1.607 FOR INTERFERENCE WITH U.S. PATENT 6,215,041 TO STICE ET AL.

Pursuant to the provisions of 37 C.F.R. §1.607, applicants respectfully request that an interference be declared between claim 19 in the subject application and claims 1-23 of U.S. Patent 6,215,041 to Stice et al. The patent is hereinafter referred to as "the Stice patent". A copy is attached as Exhibit A.

Applicants submit the following information in fulfillment of the requirements of 37 C.F.R. § 1.607.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

I. PROPOSED COUNT

In fulfillment of the requirement of Rule 1.607(a)(2), applicants propose the following Count for purposes of interference:

A method of cloning a non-human mammal by nuclear transfer comprising:

(i) inserting a nucleus of a non-human mammalian differentiated somatic cell, which has passed start in the mitotic cell cycle and is in the G1 phase of the cell cycle, into an unactivated, metaphase II-arrested, non-human mammalian enucleated oocyte of the same species to reconstruct an embryo;

(ii) maintaining the reconstructed embryo without activation for a sufficient time to allow the reconstructed embryo to become capable of developing to term;

(iii) activating the resultant reconstructed embryo;

(iv) culturing said activated, reconstructed embryo to blastocyst; and

(v) transferring said cultured, reconstructed embryo to a host non-human mammal of the same species such that the reconstructed embryo develops to term;

or:

(i) inserting a desired non-human mammalian non-quiescent somatic cell or a nucleus isolated from said non-quiescent somatic cell, into a non-human mammalian enucleated oocyte of the same species under conditions suitable for the formation of the nuclear transfer (NT) unit;

(ii) activating the resultant nuclear transfer unit;

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

(iii) culturing said activated NT unit until greater than the 2-cell developmental stage; and

(iv) transferring said cultured NT unit to a host non-human mammal of the same species such that the NT unit develops into a non-human mammal.

The Proposed Count incorporates the exact language of applicants' claim 19. The Proposed Count also incorporates the exact language of claim 20 of the Stice patent.[1]

II. IDENTIFICATION OF PATENT CLAIMS CORRESPONDING TO THE PROPOSED COUNT

Claims 1-23 of the Stice patent, which are all of the claims of the patent, are directed to methods of cloning non-human mammals or non-human mammalian fetuses by nuclear transfer. All of the patent claims are directed to the same invention and should be designated as corresponding to the Proposed Count. *See* 37 C.F.R. § 1.606.

---

[1] An Alternative Proposed Count could read as follows:

> A method of cloning a non-human mammal by nuclear transfer comprising the method of claim 19 of Campbell et al.'s application Serial No. _____ or claim 20 of Stice et al.'s U.S. Patent No. 6,215,041.

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

III. IDENTIFICATION OF APPLICANTS' CLAIMS CORRESPONDING TO THE PROPOSED COUNT

Applicants' claim 19 is also directed to methods of cloning non-human mammals by nuclear transfer. This claim should be designated as corresponding to the Proposed Count.

IV. APPLICATION OF APPLICANTS' CLAIM TO THE DISCLOSURE IN THEIR APPLICATION

Applicants' claim 19 is being presented in a Preliminary Amendment filed herewith. Section (a)(5) of Rule 1.607 requires applicants to identify support in their application for any of their claims designated as corresponding to the Proposed Count.

Exhibit B annexed hereto contains each of the recitations in applicants' claim 19 and quotations from the specification supporting each recitation. Exhibit B thus satisfies the requirement of Rule 1.607(a)(5).

V. APPLICANTS ARE THE SENIOR PARTY RELATIVE TO STICE ET AL.

The Stice patent is based on a U.S. application filed January 8, 1998. The Stice patent is related to applications filed on July 3, 1997, and January 10, 1997. If Stice et al. can demonstrate that they are entitled to the benefit of the

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

filing date of each of the earlier-filed applications as constructive reductions to practice, Stice et al.'s effective filing date for purposes of an interference would be January 10, 1997.

Applicants, on the other hand, have an effective U.S. filing date of August 31, 1995, through a series of priority applications, each of which constitutes a constructive reduction to practice of the Proposed Count. Specifically, the subject application is a continuation of parent application Serial No. 09/650,194, filed August 29, 2000, which is a continuation of grandparent application Serial No. 08/803,165, filed February 19, 1997. Thus, applicants are entitled to the benefit of the filing date of February 19, 1997, of the grandparent application because it is linked to the grandparent application through a continuation application, and thus has an identical specification to the grandparent application. 35 U.S.C. § 120.

The grandparent application, in turn, is a §371 application of PCT/GB96/02098, filed August 30, 1996. A copy of the PCT application as published under No. WO 97/07668 is attached as Exhibit C. The PCT application and the subject application are identical. Thus, applicants are also entitled to the benefit of

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

the filing date of August 30, 1996, of the PCT application. 35 U.S.C. § 119 and MPEP 1896.

Finally, the PCT application claims the benefit of British application No. 95 17779.6, filed August 31, 1995. A certified copy of the British priority application is of record in application Serial No. 08/803,165, filed February 19, 1997.

There are several differences between the British priority application and the subject U.S. application. These differences have been highlighted on Exhibit D, which is a copy of the subject application. It will be evident that the highlighted passages do not affect applicants' right to the benefit of the British application for the subject matter of claim 19 in the subject application. Thus, applicants are entitled to the filing date of their British priority application. 35 U.S.C. § 119.

In summary, applicants' effective filing date of August 31, 1995, can be traced from the subject continuation application through the parent and grandparent applications to the earlier PCT application and finally to the British priority application. Each of these applications constitutes a constructive reduction to practice of the Proposed Count. Because applicants' effective filing date of **August 31, 1995**, predates by **almost 17**

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

months the earliest filing date of **January 10, 1997**, which Stice et al. could allege, justice requires that applicants be named the senior party in any interference that may be declared with the Stice patent.

VI. APPLICANTS AND STICE ET AL. ARE CLAIMING THE SAME PATENTABLE INVENTION

Applicants' claim 19 defines the same patentable invention as claims 1-23 in the Stice patent. Thus, interference-in-fact exists. *See* 37 C.F.R. § 1.601(j). ("An interference-in-fact exists when at least one claim of a party that is designated to correspond to a count and at least one claim of an opponent that is designated to correspond to the count define the same patentable invention.")

More particularly, 37 C.F.R. § 1.601(n) provides that one invention is "the same patentable invention" as another invention when the first invention is the same as (35 U.S.C. § 102) or is obvious (35 U.S.C. § 103) in view of the second invention, assuming the second invention is prior art with respect to the first invention.

Recent precedent of the Trial Section of the Interference Division of the Board of Patent Appeals and Interferences indicates that resolution of whether an interference-in-fact

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

exists involves a two-way patentability analysis. According to the Board.

> The claimed invention of Party A is presumed to be prior art vis-a-vis Party B and vice versa. The claimed invention of Party A must anticipate or render obvious the claimed invention of Party B and the claimed invention of Party B must anticipate or render obvious the claimed invention of Party A. When the two-way analysis is applied, then regardless of who ultimately prevails on the issue of priority, * * * [USPTO] assures itself that it will not issue two patents to the same patentable invention.

Winter v. Fujita, 53 U.S.P.Q.2d 1234, 1243 (Bd. Pat. App. & Intf. 1999), reh'g denied, 53 U.S.P.Q.2d 1478 (Bd. Pat. App. & Intf. 2000).

In support of their request for declaration of an interference, applicants will describe their invention and then compare the terms in Stice et al.'s claim 20 with the corresponding terms in applicants' claim 19. This comparison will convincingly show that applicants are claiming the same patentable invention as that claimed in the Stice patent and that interference-in-fact exists.

Applicants will then show that applicants have met the one year time limit imposed by 35 U.S.C. § 135(b) by claiming this invention within one year of the issuance of the Stice patent.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

A. APPLICANTS' PIONEERING WORK INVOLVING NUCLEAR TRANSFER INTO DIFFERENTIATED CELLS LEAD TO THE CLONING OF "DOLLY" THE SHEEP

The report of the cloning of "Dolly" the sheep generated enormous attention in the scientific and general press because of its novelty and the significance of the work. This cloning work is the subject of applicants' invention.

At the time of applicants' invention, animal cloning had been achieved by genetic manipulation using nuclear transfer technology: A nucleus was removed from a donor cell, then transplanted into an oocyte whose own nucleus had previously been removed. The resulting renucleated oocyte gave rise to an animal that carried the nuclear genome of only the donor of the nucleus. The individual providing the donor nucleus and the individual that developed from the renucleated oocyte were referred to as "clones".

Nuclear transfer technology first employed a donor cell that was derived from an early embryo. The cells of the embryo had not undergone substantial division and differentiation --- the cells were totipotent, meaning that they had the potential to develop into any type of cell in an adult.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

Unlike embryo cloning, the prospect of cloning a cell from an adult seemed remote. More particularly, all animals develop from a single cell, the fertilized ovum, which gives rise to the various tissues and organs. Cells from the ovum undergo division and differentiation, which is driven by gene switching: The difference between one cell type and another is primarily in the range of genes that are active in each cell. Certain genes in the genome are "programmed" to express their proteins, leading to cell specialization at a very early stage of development within the embryo.

It was thought that a differentiated cell was committed to a specialized course of development and ultimately a specialized function. It was believed that a differentiated cell exhibited a memory for its specialized function and passed its functional characteristics on to its progeny. Prior to applicants' invention, is it was thought that once a cell became differentiated and entered a determined developmental pathway, the pathway was irreversible. No manipulation of the cell environment would, for example, cause a heart cell to differentiate into a liver cell.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

Applicants' specification describes the cause of this phenomenon as follows: "During development certain genes become imprinted i.e., are altered such that they are no longer transcribed." (Specification at page 4, lines 16-18.) Applicants discovered that the "imprint" on an adult differentiated cell can indeed be removed by "reprogramming" the cell nucleus following its transfer to the enucleated, recipient oocyte. The application of this discovery produced "Dolly" the sheep in Example 2 in the subject application by nuclear transfer from an adult differentiated cell in the G_o phase of the cell cycle.

More particularly, as described in the present application, the nucleus that is transferred to the enucleated, recipient oocyte can be taken from an adult differentiated cell. "Dolly" the sheep was produced in Example 2 using a nucleus from an adult sheep cell in the G_o phase of its cell cycle. The specification teaches that an adult differentiated cell in the G_1 phase of its cell cycle could be used as well. (See pages 16-21, *infra*, for a more detailed discussion of the cell cycle.) Nuclear transfer from the adult differentiated cell into an oocyte arrested in metaphase II gave rise to a viable sheep embryo by maintaining normal ploidy (i.e. diploidy). Activating

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

the embryo after nuclear transfer allowed the nucleus to remain exposed to the recipient cytoplasm. As explained in greater detail on pages 28-30, *infra.*, this delay resulted in nuclear reprogramming so that the renucleated oocyte could be implanted in a live animal and could develop to term.

The successful cloning of "Dolly" showed, for the first time, that the nucleus from a differentiated adult cell could be reprogrammed to become totipotent once more, just like the genetic material in the fertilized oocyte from which the donor cell had ultimately developed. This successful cloning of an adult animal forced scientists to accept that genome modifications, once considered irreversible, can be reversed, and that genomes of adult cells can be reprogrammed by factors in the oocyte to make them capable once again of differentiating into any cell type.

Applicants' claim 19 is directed to a method of cloning a non-human mammal by nuclear transfer using a differentiated cell from an adult donor.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

B. STICE ET AL. ALSO CLAIM TO HAVE INVENTED ANIMAL CLONING BY NUCLEAR TRANSFER USING DIFFERENTIATED CELLS

The Stice patent also claims a method of cloning a non-human mammal by nuclear transfer using a differentiated cell. Stice et al. describe their work as follows:

> According to the invention, cell nuclei derived from differentiated cow cells are transplanted into enucleated cow oocytes. The nuclei are reprogrammed to direct the development of cloned embryos, which can then be transferred into recipient females to produce fetuses and offspring, or used to produce CICM cells. The cloned embryos can also be combined with fertilized embryos to produce chimeric embryos, fetuses and/or offspring.

(Exhibit A at col. 9, lines 16-23.)

The importance of differentiated cells for nuclear transfer is pointedly emphasized in the Stice patent: "Again the present invention is novel because differentiated cell types are used." (Exhibit A at col. 11, lines 64-65.)

C. APPLICANTS' CLAIMED INVENTION IS THE SAME AS THE SUBJECT MATTER OF THE STICE ET AL. AS SHOWN BY A COMPARISON OF APPLICANTS' CLAIM 19 WITH CLAIM 20 OF THE STICE PATENT.

Table 2 and the comments that follow show that applicants' claim 19 contains limitations that are the same as limitations in claim 20 of the Stice patent. These are the two claims that comprise applicants' Proposed Count on pages 2-3, *supra*.

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

TABLE 2

COMPARISON OF APPLICANTS' CLAIM 19 WITH CLAIM 20 OF THE STICE PATENT.

Applicants' claim 19	Claim 20 of the Stice patent
19. A method of cloning	20. A method of cloning
a non-human mammal	a non-human mammal
by nuclear transfer	by nuclear transfer
comprising:	comprising the following steps:
(i) inserting	(i) inserting . . .
a nucleus	a nucleus
of a	isolated from . . .
non-human	[a desired non-human]
mammalian	[mammalian]
	non-quiescent
differentiated	
somatic cell,	somatic cell,[2]
which has passed start in the mitotic cell cycle and is in the G1 phase of the cell cycle,	
into an	into a
unactivated,	
metaphase II-arrested	
non-human	non-human
mammalian	mammalian
enucleated	enucleated
oocyte	oocyte
of the same species	of the same species
to reconstruct an embryo;	
(ii) maintaining the reconstructed embryo without activation for a sufficient time to allow the reconstructed embryo to become capable of developing to term;	under conditions suitable for the formation of the [sic] nuclear transfer (NT) unit;

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

Applicants' claim 19	Claim 20 of the Stice patent
(iii) activating the resultant reconstructed embryo;	(ii) activating the resultant nuclear transfer unit;
(iv) culturing said activated, reconstructed embryo	(iii) culturing said activated NT unit
to blastocyst; and	until greater than the 2-cell developmental stage; and
(v) transferring	(iv) transferring
said cultured, reconstructed embryo	said cultured NT unit
to a host	to a host
non-human	non-human
mammal	mammal
of the same species	of the same species
such that the reconstructed embryo develops to term.	such that the NT unit develops into a non-human mammal.

[2] The complete clause of Stice claim 20 reads as follows: "inserting a desired non-human mammalian non-quiescent somatic cell or a nucleus isolated from said non-quiescent somatic cell, into a non-human mammalian enucleated oocyte of the same species. . . ." (Exhibit A at col. 30, lines 52-55.)

It will be evident from Table 2 that applicants' claim 19 contains recitations that are identical to recitations in claim 20 of the Stice patent. As described in Exhibit B attached hereto, all of these recitations are supported by applicants' specification. Support for these recitations in applicants claim will not be further discussed.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

Instead, the terms in applicants' claim that are absent from Stice et al.'s claim, or appear to be different, will now be discussed. These terms are arranged below in a different order than they appear in Table 2 to facilitate an understanding of the meaning of the terms and their relation to each other. This discussion will leave no doubt that applicants and Stice et al. are claiming the same invention and that interference-in-fact exists.

(1) The recitation of a nuclear donor cell "which has passed start in the mitotic cell cycle and is in the G1 phase of the cell cycle" in applicants' claim

vs.

the recitation of a "non-quiescent" cell in Stice et al.'s claim

The nucleus for cloning the non-human mammal is taken from a particular type of non-human mammalian cell, which is referred to herein as the "nuclear donor" for the sake of brevity. Specifically, in applicants' claim 19, the nuclear donor is a cell "which has passed start in the mitotic cell cycle and is in the G1 phase of the cell cycle." Stice et al.'s nuclear donor is a cell that is "non-quiescent." The use of these terms does not impart separate patentability to either claim. Each term describes a cell that is actively dividing.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

The prosecution history of the Stice patent makes it clear that Stice et al. understood that a "non-quiescent" cell is an "actively dividing" cell. Dr. James M. Robl, one of the Stice et al. inventors, stated that:

> (7) In particular, the novel developments discovered by the inventors of this application include:
>
> (i) the successful use of cells committed to a somatic cell lineage for nuclear transfer or transplantation;
>
> (ii) the successful use of actively dividing, i.e., non-quiescent cells for nuclear transplantation; and
>
> (iii) the use of somatic cell genetic modification to produce genetically modified animals.

(Exhibit E, Declaration of James M. Robl, Ph.D. Pursuant To 37 C.F.R. §1.132 at page 3; original emphasis.)

Just as the "non-quiescent" nuclear donor cell recited in Stice et al.'s claim is "actively dividing", applicants' nuclear donor cell "which has passed start in the mitotic cell cycle and is in the G1 phase of the cell cycle" is "actively dividing." Underlying the meaning of a nuclear donor cell "which has passed start in the mitotic cell cycle and is in the G1 phase of the cell cycle in applicants' claim is an understanding of the cell cycle and an appreciation for the limited number of phases in

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

the cycle. The mitotic cell cycle is described in applicants' specification as follows.

The mitotic cell cycle has four distinct phases, G1, S, G2, and M. The beginning event in the cell cycle, called start, takes place in the G1 phase and has a unique function. The decision or commitment to undergo another cell cycle is made at start. Once a cell has passed through start, it passes through the remainder of the G1 phase, which is the pre-DNA synthesis phase.

The second stage, the S phase, is when DNA synthesis takes place. This is followed by the G2 phase, which is the period between DNA synthesis and mitosis. Mitosis itself occurs at the M phase. Quiescent cells (which include cells in which quiescence has been induced as well as those cells which are naturally quiescent, such as certain fully differentiated cells) are generally regarded as not being in any of these four phases of the cycle; they are usually described as being in a G0 state, so as to indicate that they would not normally progress through the cycle. (Applicants' specification at page 7, line 26 to page 8, line 11.) It is evident from this description that there are only four phases in the mitotic cell cycle, namely, the G1, S, G2, and M phases.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

Once a cell enters the mitotic cell cycle by passing through "start", the cell is committed to pass through the remainder of the G1 phase of the cell cycle in which the cell is actively dividing. These are the conditions recited in applicants' claim 19. This claim recites that the nuclear donor is a cell "which has passed start in the mitotic cell cycle and is in the G1 phase of the cell cycle."

Instead of reciting that the nuclear donor is a cell "which has passed start in the mitotic cell cycle and is in the G1 phase of the cell cycle," Stice et al.'s claim 20 recites that the donor cell is "non-quiescent". By not indicating which stage of the cell cycle the "non-quiescent" cell is in, claim 20 of the Stice patent reads on a nuclear donor cell in any phase of the cell cycle, namely, the G1, S, G2, or M phase. Thus, the difference between the two terms is that applicants' claim reads on the use of a nuclear donor cell actively dividing in the G1 phase of the cell cycle, whereas Stice et al.'s claim reads on a nuclear donor cell actively dividing in any one of the four phases of the cell cycle, including the G1 phase.

Applying the analysis required by the *Winter v. Fujita* case, applicants' species of an actively dividing nuclear donor cell "which has passed start in the mitotic cell cycle and is in

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

the G1 phase of the cell cycle" anticipates the Stice et al. claim embracing a "non-quiescent" nuclear donor cell that is actively dividing in any one of the four phases of the cell cycle, assuming applicants' claim is prior art to Stice et al.'s claim and all of the other claim limitations are the same. A later genus claim is never patentable over an earlier species claim. *Eli Lilly v. Barr Laboratories, Inc.*, 222 F.3d 973, 976 (Fed. Cir. 2000).

Following a similar analysis, but assuming the Stice et al. claim is prior art to applicants' claim, applicants' claim to the use of an actively dividing nuclear donor cell "which has passed start in the mitotic cell cycle and is in the G1 phase of the cell cycle" would be rendered *prima facie* obvious by Stice et al.'s claim encompassing the use of an actively dividing nuclear donor cell in one of the four phases of the cell cycle. Indeed, applicants' claim to one phase of the cell cycle may be anticipated by Stice et al.'s claim embracing a nuclear donor cell in any one of the four phases, one of which is recited in applicants' claim, because it is well established that a small genus can anticipate a species within that genus. *See, e.g., In re Petering*, 301 F.2d 676, 682, 133 U.S.P.Q. 275, 280 (C.C.P.A. 1962) (Genus of 20 compounds describes each species within the

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

meaning of § 102(b)); *In re Schaumann*, 572 F.2d 312, 316-317, 197 U.S.P.Q. 5, 9 (C.C.P.A. 1978) (Prior art disclosure embraces such a limited number of compounds closely related to one another in structure that it "provides a description of those compounds just as surely as if they were identified in the reference by name.").

In any event, the recitation of a donor cell "which has passed start in the mitotic cell cycle and is in the G1 phase of the cell cycle" in applicants' claim and the recitation of a donor cell that is "non-quiescent" in Stice et al.'s claim do not impart patentable distinctness to either claim. Both types of donor cells are "actively dividing." Thus, one claim anticipates the other claim, while the other claim at the least renders the first claim *prima facie* obvious.

(2) The recitation of a "differentiated somatic cell" in applicants' claim

vs.

the recitation of a "somatic cell" in Stice et al.'s claim

The nuclear donor in applicants' claim 19 is a "differentiated somatic cell," and the nuclear donor of Stice et al.'s claim 20 is a "somatic cell." These terms do not impart separate patentability to the claims.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

The recitation of a "differentiated somatic cell" in applicants' claim and a "somatic cell" in Stice et al.'s claim is a difference without a patentable distinction. The somatic cell of Stice et al.'s claim is a differentiated cell. This is evident from the Stice et al. patent where it is stated:

> The present invention uses differentiated cells. (Col. 9, lines 30-31.)
>
> * * *
>
> Again the present invention is novel because differentiated cell types are used. (Col. 11, lines 63-64.)

Applying the two-way unpatentability test of the *Winter v. Fujita* case, applicants' claim 19 would anticipate Stice et al.'s claim 20, and Stice et al.'s claim 20 would anticipate applicants' claim 19, assuming all of the other claim limitations were the same.

(3) The recitation of "metaphase II - arrested" in applicants' claim

Applicants' claim contains another recitation that is absent from Stice et al.'s claims, namely, that the oocyte into which the nucleus from the nuclear donor is transferred is in a particular phase of its cell cycle. It is "metaphase II-

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

arrested." The absence of this term from Stice et al.'s claim is immaterial for determining "same patentable invention".

Stice et al. teach in their specification that metaphase-II oocytes should be used for successful nuclear transfer. Specifically, Stice et al. state that:

> Additionally, metaphase II stage oocytes, which have been matured in vivo have been successfully used in nuclear transfer techniques.
>
> * * *
>
> The stage of maturation of the oocyte at nucleation and nuclear transfer has been reported to be significant to the success of NT methods. (See e.g., Prather et al., *Differentiation*, 48, 1-8, 1991). In general, successful mammalian embryo cloning practices use the metaphase II stage oocyte as the recipient oocyte because at this stage it is believed that the oocyte can be or is sufficiently "activated" to treat the introduced nucleus as it does a fertilizing sperm.

(Exhibit A at col. 12, lines 39 to 53.)

According to Stice et al., oocytes in metaphase II are the cells of choice to ensure successful nuclear transfer. Moreover, Stice et al. indicate this was known in the art.

The identification of a "metaphase II-arrested" oocyte as the recipient of the nucleus from the non-quiescent differentiated cell in the G1 phase of the cell cycle in applicants' claim and the absence of this recitation from Stice et al.'s claim does not impart separate patentability to either

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

claim applying the analysis under *Winter v. Fujita*. Specifically, assuming applicants' claim is prior art to Stice et al.'s claim and all of the other claim limitations are the same, applicants' claim would anticipate the claim of Stice et al.; applicants' claim would contain all of the limitations of the claim of Stice et al., and the additional limitation "metaphase II-arrested" oocyte in applicants' claim would not change the analysis.

Applying the test in reverse, and assuming the Stice et al. claim is prior art to applicants' claim and that all of the other limitations are the same, the recitation of a "metaphase II-arrested" oocyte in applicants' claim would have been obvious in view of the Stice et al. claim taken in view of the knowledge in the art that a metaphase II oocyte was the cell of choice for nuclear transfer.

(4) The recitation of a "reconstructed embryo" in applicants' claim versus "a nuclear transfer (NT) unit" in Stice et al.'s claim

Nuclear transfer or nuclear transplantation were known in the art prior to applicants' invention. These techniques involve the removal of a nucleus from a donor cell and transfer of the nucleus into an oocyte whose own nucleus has been removed. The resulting renucleated oocyte is referred to as a

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

"reconstructed embryo" in applicants' claim and "a nuclear transfer (NT) unit" in Stice et al.'s claim. It is evident from their respective disclosures that there is no patentable difference in these terms.

Specifically, applicants refer in their specification to the "reconstruction of mammalian embryos by the transfer of a donor nucleus to an enucleated oocyte" (page 1, lines 9-10), and to "[e]mbryo reconstruction by nuclear transfer" (page 1, line 18). These passages are exemplary of those that provide antecedent basis for the recitation of a "reconstructed embryo" in applicants' claim.

Stice et al. use the terms nuclear transfer, nuclear transplantation, and NT interchangeably. (Exhibit A at col. 9, lines 2-4). Stice et al. then define nuclear transfer and nuclear transplantation as follows:

> The term "nuclear transfer" or "nuclear transplantation" refers to a method of cloning wherein the nucleus from a donor cell is transplanted into enucleated oocytes. Nuclear transfer techniques or nuclear transplantation techniques are known in the literature. Also, U.S. Pat. Nos. 4,994,384 and 5,057,420 describe procedures for bovine nuclear transplantation

(Exhibit A at col. 8, line 63 to col. 9, line 2.)

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

It is evident that applicants and Stice et al. are each describing a renucleated oocyte formed by transfer of a nucleus from a differentiated cell even though they use slightly different terminology. Once again the difference in terminology is immaterial and does not alter the analysis under the *Winter v. Fujita* case or the conclusion that the different terminology does not make the claimed subject matter separately patentable.

(5) The recitation of "to reconstruct an embryo" in applicants' claim

Applicants' claim recites that the nucleus from the non-quiescent differentiated cell in the G1 phase of the cell cycle is inserted into the enucleated oocyte "to reconstruct an embryo". This recitation was included in the claim to specifically identify the product obtained from the nuclear transfer step.

The claim of Stice et al. does not recite "to reconstruct an embryo". Nevertheless, inherent in the Stice et al. claim is "the formation of a nuclear transfer (NT) unit" as a result of the insertion of the nucleus of the fibroblast into the enucleated oocyte.

The recitation of "to reconstruct an embryo" does not impart separate patentability to applicants' claim, nor does the absence of the corresponding term from Stice et al.'s claim

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

impart separate patentability to their claim, since the limitation is inherent in the nuclear transfer step specifically recited in the claim of Stice et al.

(6) The recitation of

"maintaining the reconstructed embryo without activation for a sufficient time to allow the reconstructed embryo to become capable of developing to term" in applicants' claim

vs.

"under conditions suitable for the formation of the [sic] nuclear transfer (NT) unit" in the Stice et al. claim

It will be evident from the description of applicants' invention that reprogramming of the nucleus from the nuclear donor is an essential step. In terms of the limitations in applicants' claims, this is achieved by "maintaining the reconstructed embryo without activation for a sufficient time to allow the reconstructed embryo to become capable of developing to term." It is during this delay in activation that reprogramming occurs and the "imprint" on the nucleus from the donor cell is erased.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

Stice et al. also describe the need for reprogramming the nucleus from the differentiated cell:

> According to the invention, cell nuclei derived from differentiated cow cells are transplanted into enucleated cow oocytes. The nuclei are reprogrammed to direct the development of cloned embryos, which can then be transferred into recipient females to produce fetuses and offspring, or used to produce CICM cells.

(Exhibit A at col. 9, lines 16-21)

Stice et al. then describe the activation step, during which reprogramming occurs, as follows:

> Preferably, the bovine cell and oocyte are electrofused in a 500 μm chamber by application of an electrical pulse of 90-120 V for about 15 μsec, about 24 hours after initiation of oocyte maturation. After fusion, the resultant fused NT units are then placed in a suitable medium until activation, e.g., CR1aa medium. Typically activation will be effected shortly thereafter, typically less than 24 hours later, and preferably about 4-9 hours later.
>
> * * *
>
> In one embodiment, NT activation is effected by briefly exposing the fused NT unit to a TL-HEPES medium containing 5 μm ionomycin and 1 mg/ml BSA, followed by washing in TL-HEPES containing 30 mg/ml BSA within about 24 hours after fusion, and preferably about 4 to 9 hours after fusion.

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

(Exhibit A at col. 13, line 64 to col. 14, line 4; and col. 14, lines 41-46.)

It is evident from these teachings what Stice et al. intended by the limitation "conditions suitable for the formation of the nuclear transfer (NT) unit" in their claim. The NT unit is activated, after a period of delay, for a period of preferably about 4-9 hours after the nucleus is transferred to the oocyte.

In summary, applicants and Stice et al. each provide a period for reprogramming the transferred nucleus. Each describes this period in functional terms in their respective claims. The difference in terminology does not impart separate patentability to the claims. The result is the same in each case.

(7) The recitation of "unactivated" in applicants' claim

Following transfer of the nucleus into the enucleated oocyte and reprogramming of the genes of the donor nucleus, the resulting renucleated oocyte is activated to resume embryonic development. Applicants and Stice et al. each require a step of "activating" the resulting reconstructed embryo or NT unit in their claims.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

Applicants' claim also recites that the enucleated oocyte is "unactivated" at the time of the nucleus is transferred from the nuclear donor. While the term "unactivated" is not recited in Stice et al.'s claim, it is inherent in the claim as the claim requires "activating the resultant reconstructed embryo." If the oocyte had already been activated, this activation step would be unnecessary.

In addition, if the oocyte had already been activated, the claim of Stice et al. should have included a step of interrupting activation in order to give meaning to the subsequent step of "activating" the resultant renucleated oocyte. The Stice et al. claim does not include a step of interrupting activation of an activated oocyte, and accordingly, the only reasonable interpretation of the claim is that the oocyte is "unactivated" when the nucleus is transferred.

The term "unactivated" oocyte, which is inherent in Stice et al.'s claim, does not patentably distinguish the claim from applicants' claim, or vice versa.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

(8) The recitation of culturing the renucleated embryo "to blastocyst" in applicants' claim versus "until greater than 2-cell developmental stage" in Stice et al.'s claim

After the nucleus from the nuclear donor cell has been transferred to the enucleated oocyte to form the reconstructed embryo or the NT unit, and the embryo has been reprogrammed and activated, the embryo is then cultured. In applicants' claim, the reconstructed embryo is cultured "to blastocyst," whereas in Stice et al.'s claim the embryo is cultured "until greater than the 2-cell developmental stage." This is another difference that does not impart patentable distinctness to either claim.

Expansion of an embryo "to blastocyst" generally involves about 32-cell developmental stage. Thus, culturing the reconstructed embryo to blastocyst is within the range of "until greater than the 2-cell developmental stage" in the Stice et al. claim.

Carrying out the analysis of *Winter v. Fujita*, and assuming all of the other claim limitations are the same, applicants' claim to culturing the reconstructed embryo "to blastocyst" would anticipate Stice et al.'s claim to culturing the embryo "until greater than the 2-cell developmental stage", since the limitation in applicants' claim falls within the broader range of Stice et al.'s claim. See, *Eli Lilly*, *supra*.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

Neither applicants nor Stice et al. have indicated in their respective disclosures that there is any criticality to culturing "to blastocyst" or culturing "until greater than the 2-cell developmental stage." Thus, carrying out the analysis in reverse with the Stice et al. claim being prior art to applicants' claim, it is believed that applicants' claim to culturing the reconstructed embryo "to blastocyst" would be *prima facie* obvious in view of the Stice et al. claim of culturing the embryo "until greater than the 2-cell developmental stage" because the claim limitations overlap and there is no apparent difference in the result obtained using either condition.

(9) The recitation of "such that the reconstructed embryo develops to term" in applicants' claim versus "such that the NT unit develops into a non-human mammal" in Stice et al.'s claim

To complete the cloning process, the embryo is transferred to a non-human mammal where it is allowed to develop. Applicants' claim recites that "the reconstructed embryo develops to term." The Stice et al. claim recites that "the NT [unit] develops into a non-human mammal." Once again, these

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

semantic differences are immaterial for purposes of separate patentability.

The Stice et al. claim requiring that "the NT [unit] develops in to a non-human mammal" implies that a live birth occurs, whereas applicants' claim only requires that "the reconstructed embryo develops to term," which implies the full development of a fetus, but not necessarily a live birth.

Before the "NT develops in to a non-human mammal," the NT would have had to develop to term as recited in applicants' claim. Thus, under the analysis of the *Winter v. Fujita* case, assuming all of the other claim limitations are the same, the Stice et al. claim to a live birth would anticipate applicants' claim to the development of the embryo "to term" because the Stice et al. process would have produced an embryo that developed to term before the live birth.

Thus, applying the analysis in reverse leads to a similar conclusion on the lack of separate patentability. Applicants' claim reciting development to term would render obvious the Stice et al. claim reciting development into a non-human mammal assuming all of the other claim limitations were the same. The expression "such that the reconstructed embryo develops to term" in applicants' claim and the recitation "such that the NT unit

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

develops into a non-human mammal" in the Stice et al. claim do not impart separate patentability to either claim.

In summary, the comparison of applicants' claim 19 with claim 20 of the Stice patent shows that most of the claim limitations are identical and the others do not impart separate patentability to either claim. The only conclusion is that these two claims define the same patentable invention and that interference-in-fact exists.

B. APPLICANTS HAVE MET THE ONE YEAR TIME LIMIT IMPOSED BY 35 U.S.C. § 135(b) BY CLAIMING THE SAME PATENTABLE INVENTION AS STICE ET AL. WITHIN ONE YEAR AFTER THE STICE PATENT ISSUED

The Stice et al. patent issued on **April 10, 2001.** Applicants are presenting claim 19 in the subject application in the Preliminary Amendment filed herewith. Applicants thus claimed the interfering subject matter within one year after the Stice patent issued, thereby meeting the one-year time limit imposed by 35 U.S.C. § 135(b).

VII. CONCLUSION

It is a fundamental principle that issuance of two patents for inventions that are either identical to or not patentably distinct from each other must be avoided. M.P.E.P. 2306, *citing Aelony v. Arni*, 547 F.2d 566, 192 U.S.P.Q. 486 (C.C.P.A. 1997). This mandate has a matter of urgency attached to it in the

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

present case in which a patent has already been issued to an entity that would be the junior party in an interference with applicants. An interference should be declared, and applicants should be designated as the senior party in the interference.

If there are any fees due in connection with the filing of this Request, please charge such fees to our Deposit Account No. 06-0916.

Respectfully submitted,
FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Date: November 21, 2001

By: 

Kenneth J. Meyers
Reg. No. 25,146
Tel: (202) 408-4000
Fax: (202) 408-4400
Email: ken.meyers@finnegan.com

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000